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## Perspective

# Multiple confounders influence the association between low-grade systemic inflammation and musculoskeletal pain. A call for a prudent interpretation of the literature

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Our understanding of the multiple systems and their interactions that contribute to musculoskeletal pain has evolved considerably in recent years. There is a considerable interest in the role of the immune system in both acute and persistent musculoskeletal pain states [1,2]. Systemically elevated levels of proinflammatory cytokines and chemokines have been revealed in people with musculoskeletal pain. This low-grade inflammation has been demonstrated in various musculoskeletal conditions, such as low back pain [1], neck pain [2], and radicular pain [3]. In addition, levels of inflammatory biomarkers are associated with pain severity in people with neck and shoulder pain [4] and low back pain [1]. Moreover, an initial study suggests that inflammatory responses in the acute phase of low back pain may also be related to recovery [5].

In people with and without musculoskeletal pain, levels of inflammatory biomarkers are influenced by multiple factors, such as demographic variables (eg, age and gender), lifestyle factors (eg, physical activity, saturated fat intake, and sleep quality), psychological factors (eg, depression and catastrophizing), and various diseases (eg, cardiovascular and osteoarthritis) [6–8]. These factors can increase systemic cytokine concentrations via their direct or indirect action on immune cells and the subsequent release of inflammatory cytokines and chemokines [7]. Therefore,

adjustment for potential confounders is essential to determine the level of association between low-grade systemic inflammation, musculoskeletal pain, and recovery.

The importance of adjusting for confounders when measuring systemic cytokine levels is illustrated in a study in people with multisite persistent pain [6]. In an unadjusted analysis, systemic levels of CRP, IL-6, and TNF- $\alpha$  (all proinflammatory biomarkers) were significantly higher in people with persistent multisite pain. However, after correcting for sociodemographic variables, TNF- $\alpha$  levels were no longer significantly higher. Subsequently, after correcting for lifestyle, disease, anxiety, and depression, CRP and IL-6 were no longer significantly associated with pain. Similarly, in a study of people with persistent low back pain, IL-6 levels were no longer significantly associated with affective pain after correction for sleep quality [1]. These studies demonstrate that the association between inflammatory biomarkers and the presence of musculoskeletal pain is potentially confounded by sociodemographic variables, lifestyle and disease, and anxiety and depression.

Levels of inflammatory biomarkers likely arise from a complex interplay among the central nervous system, immune system, endocrine system, psychological factors, sociodemographic factors, lifestyle, and behavior. In most studies, it will not be feasible to correct for all possible confounders or to add all effect modifiers in the association model when assessing the relationship between inflammatory biomarkers and musculoskeletal pain or patient recovery. However, we must remain vigilant when assessing and interpreting associations between systemic cytokine concentrations with persistent musculoskeletal pain and recovery. Unfortunately, researchers rarely control for these

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confounding factors in the analyses, or only control for a small subset of confounders. This may result in incorrect or overly optimistic conclusions. To address the common issue of insufficient power to include all potential confounding variables, we propose to create a core set of confounders that researchers need to correct for in future multiple regression analyses. This set of confounders can also be used when deriving a model to predict musculoskeletal pain or recovery that includes inflammatory biomarkers as possible predictor variables. Further insight in the interplay between pain, low-grade inflammation, and confounders will result in a better understanding of pain mechanisms and potential treatment options for people with or at risk of developing persistent musculoskeletal pain.

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